

SUMMARY MINUTES

OF THE

CIRCULATORY SYSTEM DEVICES

ADVISORY PANEL MEETING

OPEN SESSION

JULY 9-10, 2001

**Gaithersburg Marriott Washingtonian Center
9751 Washingtonian Boulevard
Gaithersburg, Maryland**

CIRCULATORY SYSTEM DEVICES ADVISORY PANEL MEETING

July 9-10, 2001

ATTENDEES

CHAIRPERSON (July 9 only)

Cynthia M. Tracy, M.D.
Georgetown University Hospital

ACTING CHAIRPERSON (July 10 only)

Julie Swain, M.D.
NASA

EXECUTIVE SECRETARY

Megan Moynahan, M.S.
Food and Drug Administration

VOTING MEMBERS

Salim Aziz, M.D. (July 10 only)
University of Colorado

Warren K. Laskey, M.D.
University of Maryland School of Medicine

Janet T. Wittes, Ph.D.
Statistics Collaborative, Inc.

CONSULTANTS

Mitchell Krucoff, M.D.
Duke University Medical Center

Michael Domanski, M.D.
NIH/NHLBI

Thomas Ferguson, M.D. (July 9 only)
Washington University School of Medicine

Francis Klocke, M.D. (July 9 only)
Northwestern University Medical School

Ted Kaptchuk, O.M.D.
Center for Alternative Medicine Research
BIDMC, Harvard Medical School

Ileana Pina, M.D.
Case Western Reserve University/University
Hospital of Cleveland

Jeff Borer, M.D. (July 9 only)
New York Presbyterian Hospital /Cornell
University Weill Medical College

Mark Haigney, M.D. (July 10 only)
University of the Health Sciences

CONSUMER REPRESENTATIVE

Robert A. Dacey

INDUSTRY REPRESENTATIVE

Michael C. Morton
W.L. Gore & Associates

FOOD AND DRUG ADMINISTRATION

James E. Dillard III
Larry Kessler
Donna-Bea Tillman
Bram Zuckerman, M.D.
Helena S. Barold, M.D.
Lesley L. Ewing, M.D.
Michael J. Berman, Ph.D.
Mitchell J. Shein
Gerry Gray, Ph.D.

OPEN SESSION—July 9, 2001

Cynthia M. Tracy, M.D., Panel Chairperson, called the Open Session to order at 10:07 a.m., stating that the morning session would consist of an update for the panel on endovascular grafts. **Executive Secretary Megan Moynahan** read the conflict of interest statement and noted that waivers had been granted to Janet T. Wittes, Ph.D., and Jeff Borer, M.D., for their interests in firms potentially affected by the day's session. Matters concerning possible conflicts for Janet T. Wittes, Ph.D., Jeff Borer, M.D., Cynthia M. Tracy, M.D., Warren K. Laskey, M.D., Francis Klocke, M.D., Ileana Pina, M.D., and Mitchell Krucoff, M.D., had been also considered but deemed unrelated to the day's agenda, and their full participation would be allowed. **Ms. Moynahan** also read appointments to temporary voting status for Mitchell Krucoff, M.D., Michael Domanski, M.D., Thomas Ferguson, M.D., Francis Klocke, M.D., Ted Kaptchuk, O.M.D., Ileana Pina, M.D., and Jeff Borer, M.D. **Dr. Tracy** asked the panel members to introduce themselves and state their areas of expertise.

FDA Presentations

James E. Dillard, Director, Division of Cardiovascular and Respiratory Devices, provided regulatory background and an update on two approved premarket approval applications (PMAs) for endovascular grafts—the Guidant Endovascular Solutions Ancure Endograft System (P990017) and the Medtronic AVE AneuRx Stent Graft (P99000220). Recent developments have made clear the need for greater follow-up on clinical issues involving patient selection,

proper deployment, and monitoring, as well as on device integrity and manufacturing issues. On January 24, 2001, Medtronic issued a performance update with information on proper clinical use and manufacturing status, saying its device remained safe and effective. In March 2001, Guidant began a voluntary halt and recall in March of 2001 of its non-implanted devices based on regulatory deficiencies primarily due to deployment. Both companies continue to work closely with the FDA, as both industry and the Agency recognize the need for longer-term clinical and device-related follow-up on these devices and for postmarket surveillance through registry data.

Larry Kessler, Sc.D., Director of the Office of Surveillance and Biometrics, discussed the FDA's mandatory Medical Device Reporting (MDR) Program, explaining its purpose, scope, and limitations. Mr. Kessler showed a breakdown of the adverse event reports of death, serious injury, and malfunction involving the AneuRx and Ancure devices, noting that the problems were different for each product. Mr. Kessler discussed the postmarket study authorities granted to FDA for postmarket surveillance of PMAs and 510ks, which are seen as a complement to the FDA's premarket program. He stated that a postmarket study order was issued to Medtronic on June 13, 2001 to compare postmarket to premarket patient populations for the AneuRx device, to compare postmarket to premarket types and rates of adverse events, and to look at compliance rates with follow-up and types of imaging. Mr. Kessler noted that the American College of Cardiology and other involved centers recently discussed postmarket follow-up on cardiovascular products and the use of the Lifeline registry as one model to collect postmarket data.

Open Public Hearing

Beverly Huss, CEO and President of Guidant Endovascular Solutions, discussed the history of Guidant's Ancure device, which has been on the market since 1999. After internal audits showed problems with delivery system changes, deployment techniques, packing integrity, and MDR reporting issues, the company outlined steps to the FDA to resolve the issues, all of which have been implemented. The company used a strict interpretation of the guidelines and a very conservative standard for reporting all MDRs and deployment issues, and Ms. Huss asked the FDA to hold all companies to this standard. She stated that the clinical data remain unchanged and long-term safety of the Ancure device is not at issue.

Don Schwarten, M.D., Chief Medical Officer of Guidant Endovascular Solutions, provided a clinical update on the Ancure device, noting that there has been no AAA rupture in over 7500 bifurcated Guidant implants. He stated that there has been consistently good clinical performance of the bifurcated implant throughout the device's history and that the majority of deployment issues have been addressed.

Christopher K. Zarins, M.D., Chief of the Division of Vascular Surgery of the Stanford School of Medicine and a consultant to Medtronic, discussed the history of the AneuRx stent graft, listing the publications and abstracts produced during its clinical trials. He discussed the U.S. AneuRx clinical trial and provided details and context on the 25 ruptures that have occurred in the five-year experience of AneuRx worldwide, noting that most were due to low placement or poor patient selection. Dr. Zarins also showed statistics indicating that the stent

graft is effective in preventing aneurysm rupture and reduces the morbidity of aneurysm repair and the risk of aneurysm-related death compared to open surgery.

Tom Wilder, Vice President and General Manager of Endovascular Stent Grafts, of Medtronic, stated that Medtronic is committed to working with physicians and regulatory agencies to further develop and improve this treatment option for patients, to training and education, to monitoring product performance, and to advancing the technology.

Rodney White, M.D., of the Harbor-UCLA Medical Center, discussed the Lifeline Registry and postmarket surveillance. He explained the development of the registry as a way to follow IDE patients with devices from various manufacturers. The registry now consists of 1650 patients with an average of three-to-five years of follow-up, which provides a mature data set to answer device and procedure-related questions. The registry has a website (Lifeline Registry.com) to which additional data can be added.

Kim Hodgson, Professor and Chairman of the Division of Vascular Surgery at Southern Illinois University, expressed his personal views on aortic endografts, stating that it is a good but immature technology that still needs study and oversight to ensure that it does not harm patients. He argued that distribution of these devices should be limited to a finite number of centers of excellence that have demonstrated skills in patient selection, implantation, and post-procedure management. New endograft applications for approval should be subjected to similar limited commercialization until the evolutionary process is further along.

PMA P970029/S004—Eclipse Surgical Technologies, Inc. Percutaneous Myocardial

Revascularization (PMR) Holmium Laser System

Open Public Hearing

Dr. Tracy invited those present to address the panel. There were no requests to speak.

Sponsor Presentation

Richard Lanigan, Vice President for Government Affairs for Eclipse, provided the technological background, comparing transmural myocardial revascularization (TMR) to the percutaneous (PMR) approach.

Patrick L. Whitlow, M.D., Director of Interventional Cardiology at the Cleveland Clinic, explained the design and methodology of the two randomized clinical trials on the PMR system. The PACIFIC study was a prospective, randomized, multicenter study in the United States of PMR with medical care against a control group that received medical care alone. The BELIEF study was a prospective, double blinded, randomized study in Norway of the device against a sham procedure. Dr. Whitlow explained the PACIFIC study design and listed the eleven U.S. investigational centers. Primary effectiveness endpoints were improvement of two or more classes in angina and change in exercise duration (ETT), with a secondary endpoint of improvement in quality of life. Safety measures were mortality and incidence of adverse events. Dr. Whitlow listed patient inclusion and exclusion criteria and accountability procedures for the 100 patients in each arm. Baseline characteristics of both groups were similar, with most having had many prior interventions.

Results of the PACIFIC study showed a shift toward lower classification of angina for both groups when assessed by investigator, with a significantly greater number of the investigational device group improving two classes or more at 12 months when assessed by investigator and a less significant number still benefiting the investigational device when assessed independently. Both groups showed improvements at 12 months in the exercise tolerance test, with no significant increase for device over control. Improvements in quality of life as measured by the Seattle Angina Questionnaire (SAQ) showed a statistically significant and dramatic improvement for the device group at 12 months and an improvement in angina stability at 12 months.

Dr. Whitlow itemized serious adverse events for the PMR patients, noting that such events are expected in this medically refractory patient population and may be minimized by rigorous training, patient selection, and labeling. Although safety results as measured by patients with serious cardiac adverse events at 12 months with angina removed showed higher total numbers of events for the investigational group, Dr. Whitlow concluded that these were reasonable procedural risks for seriously ill patients with limited treatment options.

Dr. Whitlow also discussed the BELIEF study, which compared the device with medical therapy to a sham procedure plus medical therapy. He explained the design of the study, which was a randomized, controlled, double-blinded study of 82 patients at two Norwegian centers. Blinding procedures were discussed, as were baseline and procedural characteristics. Effectiveness outcome measures were the same as in the PACIFIC study. Improvement in angina

scores was greater for the PMR group at three and six months than for the sham group, although the improvement was not as great or as significant as in the PACIFIC study. The numbers of adverse events for PMR and sham groups were not statistically significantly different. Dr. Whitlow stated that safety and efficacy of the PMR system are confirmed by the BELIEF study results and that the study establishes that angina improvement in the PMR treated group is not primarily due to placebo effect.

William O'Neill, M.D., Director of Interventional Cardiology at the William Beaumont Hospital, discussed risk/benefit considerations of PMR. He looked at the public health impact of improvement for this group of candidates with very poor quality of life, stressing that this procedure is not an alternative to traditional revascularization but is indicated for a select patient group. He read the proposed indication for use and noted that the majority of this patient population achieved a two-class improvement in angina symptoms, a significant reduction in hospitalizations for angina, a significant improvement in ETT duration, and a significant improvement in quality of life. Dr. O'Neill thought the procedure showed similar angina improvement at 12 months to that of TMR, but added that TMR is a long, open procedure with lengthy recuperation time. After listing labeling recommendations for managing procedural risk and for training physicians, he concluded that there is overriding evidence of decreased angina and related hospitalization and that the consistency of study results establishes that angina improvement in the PMR group is not primarily due to placebo effect.

FDA Presentation

Michael Berman, Ph.D., introduced the FDA review and described the device. He stated that appropriate preclinical testing addressed engineering, biocompatibility, and sterility issues, and there are no remaining preclinical concerns.

Lesley Ewing, M.D., presented the clinical review of the PACIFIC and BELIEF studies. After describing the PACIFIC study, she showed data on patients with serious cardiac adverse events at 12 months, noting that when data for angina are removed, the total for the PMR group is higher than that for control. She presented sponsor data on angina improvement at 12 months of more than two classes of angina, showing that independent assessment produces a less favorable outcome than did investigator assessment. Both PMR and control groups showed improvement at 12 months in ETT, with no statistical advantage for the PMR group. Similarly, all showed a significant improvement in quality of life at 12 months, with the PMR group showing statistically significant improvement over the control group.

Dr. Ewing also described the BELIEF study, noting that in this study, unlike PACIFIC, the number of patient with peri-procedure adverse events in this study was essentially the same in PMR and control groups. In both studies, improvement in angina class favored the PMR group, especially at the six-month point. SAQ results for the BELIEF and PACIFIC studies differed, with the PACIFIC SAQ results showing an improvement from baseline in treated patients compared with medical management, while in the BELIEF study, only angina stability results improved significantly.

Dr. Ewing looked at patient population differences between the two studies, noting that both were medically refractory, but found no differences to explain differences in study results. She summarized that the cardiac adverse event rate (minus angina) in treated patients versus controls was higher in PACIFIC but not in BELIEF. In both studies a significant percentage of the treated patients had an improvement of two or more angina classes compared with the control patients. In the PACIFIC study there was an improvement in SAQ scores from baseline in treated patients compared with medical management, which was not seen in BELIEF, except in one subscore. Exercise duration improved with PMR in PACIFIC but not in BELIEF, but the studies used different exercise protocols. And finally, in both studies some patients improved their angina scores without PMR treatment. Mr. Berman read the FDA questions for panel discussion.

Open Committee Discussion, Recommendations, and Voting

Thomas Ferguson, M.D., was the lead panel reviewer. He thanked the sponsors for their lucid presentation of complicated data. He asked sponsors for data on the mechanism of intervention or on the number of penetrations needed to be effective and on the correlation of interventions with results. He asked if there were histological studies or objective data on patients who died.

Other panel comments focused on the power of the study, with particular concern that in a study powered to show mortality there was still a strong trend toward mortality in the device group. Several members commented that in the absence of understanding about the mechanism

of PMR, there is an obligation to be meticulous about safety and efficacy data. Several members agreed that if angina relief is an efficacy endpoint, it should be subtracted from the safety evaluation. Others expressed doubts that the BELIEF study resolved the issue of placebo effect. There was concern that one-year data may not be enough with these data and this group of patients and that the study was underpowered to look at safety issues. The panel saw some indication that the device reduces angina pain but was unsure how to quantify this benefit and balance it against the device risk. The benefit of pain reduction against possible adverse events was difficult to quantify or express accurately in advising patients whether to have the procedure.

Industry Representative Michael L. Morton reminded the panel to vote on the basis of reasonable assurance of efficacy and safety, and not on the basis of what they would have preferred in a study design. **Consumer Representative Robert A. Dacey** was troubled about the complexity of physician/patient instructions when the mechanism of device action is unknown and when the risk/benefit analysis is unclear.

Sponsor Remarks

Mr. Lanigan urged the panel to focus on the fact that this is another option for treating medically refractory patients with a lower risk than the surgical option. He stated that the BELIEF study showed the device produces a more than a placebo effect.

FDA Questions to the Panel

1a. The total of serious arrhythmias, heart failure, MI, thromboembolic events, and deaths in PACIFIC was higher for treated than for control patients. In BELIEF there was only one such

adverse event in the treated patients. Please discuss the implications of these findings for the assessment of safety.

The panel was not sure that safety had been demonstrated, particularly in the PACIFIC trial, saying that there was a risk indicated, of unknown magnitude, of adverse events that can happen later. This risk was difficult to quantify, given the sample size and discrepancies and disagreements over how angina complications should be categorized, but was nonetheless evident. The panel was not reassured by the better safety results of the BELIEF trial, saying that this less medically challenging population also showed less evidence of benefit in any risk/benefit analysis.

1b. Please discuss the clinical importance of the adverse events observed in these patients.

The panel expressed considerable concern about the adverse events observed in the PACIFIC trial and stated its conviction that there is an even greater obligation to demonstrate robust safety results in a trial that compares use of an invasive procedure with an unknown mechanism of effect versus standard medical treatment.

2a. Please discuss the possible impact of investigator bias on the evaluation of improvement in CCSAS scores in the PACIFIC trial (as opposed to the independent assessment made in the BELIEF trial).

The panel did have some concern about bias, despite the reassurance of independent assessment in the BELIEF results, because of the need for objective corroboration of subjective endpoints such as relief of chest pain and because of the discrepancy in outcomes. The panel agreed there

was room for concern, ranging from possible bias to mixing of endpoints that are more concrete with others that are more subjective.

2b. The percent of patients meeting the criteria for improvement in CCSAS, SAQ, and ETT were all significantly greater for treated than for control patients in PACIFIC. In BELIEF treated patients outperformed controls for CCSAS but not for SAQ or ETT. Please discuss this apparent difference.

The panel acknowledged there is a mismatch in results and was not sure how it could be reconciled. Some argued that results from BELIEF should be given greater emphasis because assessment was blinded. It was agreed that the angina results show improvement, but the discrepancies between the study results are still hard to reconcile, especially given that the angina results are not as reliable as ETT results. It was suggested that sponsors look at a trivariate tailed trial, showing when improvements in angina score and ETT and SAQ are correlated and when they are not, without mixing the data.

2c. CCSAS and SAQ scores both assess aspects of angina. In PACIFIC a higher percentage of treated patients (versus controls) showed improvement in CCSAS and SAQ. In BELIEF this was true for CCSAS but not for SAQ. Please discuss this apparent difference.

The panel thought this issue had been adequately addressed, adding that contradictory results do happen.

3. Please comment on the improvement in angina in some control patients in each study as it relates to the effectiveness of PMR as a treatment for angina.

The panel observed that the nature of coronary disease is not static and that it is common to have some improvement in control patients in any coronary trial. This fact does not change the BELIEF or PACIFIC results, although the panel noted that in the absence of a known mechanism, the need for robust data and for minimizing measurement errors is acute.

4. Please comment on the inclusion or exclusion of patients who received “reintervention.”

Should these patients be counted as failures of PMR?

The panel recommended that these patients should be counted as failures of PMR.

5. Please discuss whether the data in the PMA supplement provide reasonable assurance of effectiveness for this device in the patient population studied.

The panel was not sure how to reconcile the data set, given that there are some data showing effectiveness of the device in angina reduction, but other data do not show effectiveness.

6a) The indications portion of the labeling states that this device is indicated to “increase exercise tolerance.” Please comment on whether the information presented today provides adequate justification for this claim.

The panel was not comfortable with including this wording on increasing exercise tolerance in the labeling.

6b) Please provide any other recommendations or comments regarding the indications statement and/or any other aspects of the labeling of this device.

The panel recommended that the FDA remove from the labeling any implication that the device improves the underlying physiology and to make explicit that it is only for symptomatic relief of

angina. The panel also recommended that angina data be separated from other events requiring hospitalization in Table 1 and that the risk/benefit ratio be clarified.

7. Please identify and discuss the items that you believe should be contained in a physician's training program for this device.

The panel recommended stating clearly that the device is for anginal improvement in the specified population without addressing the underlying mechanism of disease, that this device is for patients with inoperable coronary conditions, and that exercise tolerance data are not clear-cut.

8a) Is additional clinical follow-up of the PMA cohort needed to evaluate the long-term effects of PMR?

The panel stated that additional clinical follow-up of the PMA cohort is needed.

8b) Please discuss the possible use of PMR in combination with other modalities. Would additional clinical trials be appropriate?

The panel thought it very important to do more work on PMR before releasing the device and that PMR cannot be combined with other modalities at this point.

Closing Sponsor Comments

Sponsor representatives stated that there was a strong association between improvement in angina and improvement in ETT results in data from the PACIFIC trial 12-month follow-up.

Closing FDA Comments

The FDA had no additional remarks.

Industry Representative Michael C. Morton asked for clarification on the final question, noting that there were no data presented on combining modalities. **Mr. Dillard** explained that the FDA was seeking guidance on whether data on the patient population studied for this device could be expanded for use with other modalities.

Recommendations and Voting

Panel Executive Secretary Megan Moynahan read the voting options and instructions.

A motion was made and seconded to recommend the PMA as not approvable. This motion passed by a vote of seven to two. The panel suggested that further study be done with more data collection, increased patient numbers, and longer follow-up in the population already studied to show a more robust approach toward demonstrating safety.

Open Public Hearing

There were no requests to address the panel.

Dr. Tracy thanked the sponsors and adjourned the session for the day at 5:30 p.m.

OPEN SESSION—July 10, 2001

Acting Panel Chairperson Julie Swain, M.D., called the session to order at 8:02 a.m. and read the panel the charge for the morning, to review a PMA from Guidant Corporation for the Contak CD and Easy Trak Lead System. She asked the panel to introduce themselves and state their area of expertise. **Panel Executive Secretary Megan Moynahan** read the conflict of interest statement, noting that Salim Aziz, M.D., Warren K. Laskey, M.D., Mitchell Krucoff, M.D., Mark Haigney, M.D., and Ileana Pina, M.D., had reported interests

in firms at issue in the day's deliberations but on matters unrelated to the agenda. Their full participation was allowed. Because of regulations governing covered relationships, Panel Chairperson Cynthia Tracy would not participate in the session. Ms. Moynahan also read the appointment to voting membership for Mitchell Krucoff, M.D., Michael Domanski, M.D., Julie Swain, M.D., Ted Kaptchuk, O.M.D., Ileana Pina, M.D., and Mark Haigney, M.D., and an appointment for Julie Swain, M.D. as Acting Chairperson for the duration of the meeting.

Dr. Bernard Statland, Director of the Office of Device Evaluation, welcomed the panel and thanked its members, the FDA staff, and industry representatives.

Open Public Hearing

Dr. Swain invited those present to address the panel. There were no requests to speak.

Sponsor Presentation: Guidant Corporation P010012, Contak CD and Easy Trak Lead System

Dale DeVries, Vice President for Clinical and Regulatory Affairs for Guidant, stated that this was the first PMA for cardiac resynchronization therapy (CRT) in combination with a proven ICD therapy. He described the challenges of new therapy trials and outlined the study chronology, into which multiple changes were incorporated. Mr. DeVries summarized that the clinical trial showed the device and procedure to be safe and, while it did not achieve its primary effectiveness endpoints, the trial did identify a subgroup of patients that clearly benefited from the therapy.

Patrick Yong, principal clinical research associate for Guidant, discussed the role of CRT for dilated cardiomyopathy and the method of lead placement in the left ventricle. He showed the Contak device and explained how it functions through biventricular sensing and stimulation. Mr. Yong described the preclinical testing for the system, which included design validation, safety and risk analysis, biocompatibility evaluation, and animal studies.

Mr. Yong explained the design of the clinical study, which was a randomized trial of 1082 patients at 47 centers, and listed entry criteria. Phase I of the original study sought to establish whether CRT improves chronic functional status through a randomized, double blinded, crossover study of 248 patients needing ICDs, with an exercise test to determine functional status at three and six months. The revised Phase II study design was modified to meet the FDA requirement of six months of continuous data and was based on a new hypothesis of seeing whether the device would slow heart failure progression, with morbidity and mortality as the primary outcomes.

Mr. Yong explained the patient demographics and study endpoints. Safety of the lead was assessed in terms of lead-related adverse events, with that rate within the defined safety standards. Lead effectiveness was determined by performance and implant success rate and met the defined endpoints. For the system itself, safety endpoints were severe device-related adverse events and operative mortality. Effectiveness endpoints for the system were slowing the progression of heart failure as defined by a composite of variables, improvement in

functional status by various measures, quality of life, change in NYHA functional class, ATP conversion efficacy, and VT detection time.

Mr. Yong summarized that statistical significance was not reached for the primary or secondary endpoints. Event analysis showed a positive directional effect on the composite index with no evidence of harm. There was also a trend toward improvement in peak VO₂, six-minute walk, NYHA class, and quality of life. Covariate analysis and data from other studies found a patient population that does benefit from the device in Class III and IV heart patients. Observed CRT effects are concordant with other studies and consistent with them. The lead, system, and CRT are safe for the entire population studied, including the advanced heart failure group. The lead and the system are effective for the entire population and for advanced heart failure population. CRT is effective for the advanced heart failure group.

Michael Higginbotham, M.D., of the Cardiopulmonary Core Lab, discussed clinical relevance of the findings. He explained why the endpoints selected, such as peak VO₂, the six-minute walk, quality of life and NYHA class symptoms, were appropriate. Dr. Higginbotham also discussed what clinically meaningful improvements for these patients would be and showed how an increase in oxygen uptake would correlate with an important increase in ability to perform daily functions. He looked at the concordance of functional measures, showing the uniqueness of CRT in comparisons with pharmacological studies of heart failure. Dr. Higginbotham summarized that the endpoints selected were appropriate and complementary and that CRT benefited patients with advanced heart failure. Changes were

positive and internally consistent and results compared favorably with those in other heart failure studies. The improvement seen in functional status is clinically important.

FDA Presentation

Helen S. Barold, M.D., introduced the FDA review team for the PMA. The first two PMA modules, which involved manufacturing information and nonclinical studies, have been successfully completed. The third covers clinical study data, which she presented after a description of the device and its intended use. She listed primary and secondary study endpoints and statistical analysis methods used for each. Dr. Barold explained the inclusion and exclusion criteria, baseline characteristics, and change in NYHA class from baseline to randomization, with particular attention to the baseline characteristics of the advanced heart failure group who ultimately benefited most from the device.

Gerry Gray, Ph.D., FDA statistician, explained the two different subgroup analyses that were submitted, the non-right bundle branch block patients and the advanced heart failure subgroup, and listed other covariates considered. He expressed concern about use of NYHA class as a covariate because valid statistical covariates are not dependent on treatment and results are difficult to interpret if covariates are affected by treatment. He also warned against a general tendency to overinterpret the significance of subgroup analysis, particularly when multiple subgroups are analyzed, and raised questions about the statistical significance of the advanced heart failure subgroup.

Dr. Barold presented data on the composite endpoint, primary study endpoints, and composite endpoint for the advanced heart failure subgroup, as well as on deaths. She showed results on peak VO₂, change in VE/VCO₂, quality of life, and six-minute hall walk for both control and CRT system, for individual results, and for the advanced heart failure subgroup. NYHA functional class improved for both CRT and non-CRT groups, but there was no statistically significant difference. Dr. Barold also presented results on APT conversion efficacy, ventricular fibrillation detection time, severe device-related adverse events and operative mortality, hospitalizations for heart failure, lead safety, and coronary sinus trauma. She concluded that the device met all preclinical and manufacturing requirements and safety and lead performance endpoints. It did not satisfy effectiveness endpoints when all patients were evaluated, although in the advanced heart failure subgroup, there were more improvements with CRT in most functional endpoints. Dr. Barold read the FDA questions for panel review.

Open Committee Discussion

Michael Domanski, M.D., was the primary panel reviewer. He complimented the FDA on its review and expressed real concerns about the study, saying the sponsor had not demonstrated efficacy. He expressed doubts about the trial design and lack of demonstrated benefits in the endpoints selected. Dr. Domanski also suggested that benefits seen in the advanced heart failure group were a data-driven post-hoc analysis. He asked for more detail on the two deaths caused by coronary sinus perforations, calling that a misadventure of

substantial proportion. Dr. Domanski added that while this may be a useful therapy with a clinical application, it is a very specific device not doing the tasks assigned and his concern relative to this indication was not allayed.

Other panel comments focused on concern that the subgroup analysis was problematic and on safety issues. Several indicated that they thought this was an important potential therapy for a patient population in need of help but that safety and efficacy were not demonstrated. Concerns were expressed about the coronary sinus safety data and about the difficulty of randomizing patients who may achieve a different NYHA classification between baseline and randomization. Another issue involved the lack of six-month or longer data and whether the amount of data was sufficient for analysis.

FDA Questions

1a. Please discuss potential safety issues associated with implantation of a third lead in the coronary venous system and comment on whether the data in the PMA support the safety of the lead system for the proposed indication.

The panel agreed that the lead system is safe in the FDA sense but wanted a clearer indication of when to implant it.

1b. Please discuss the clinical importance of the overall adverse events, complications, and observations, and comment on whether the data in the PMA provide reasonable assurance of the safety of this device system.

The panel consensus was that the data did not provide such assurance.

2a. Please discuss the clinical relevance of the effectiveness endpoints for this patient population.

The panel thought these endpoints were reasonable.

2b. Please comment on whether six-month follow-up is adequate to provide a reasonable estimate of device safety and effectiveness.

The panel thought that 12-month data would be useful, but relevant and convincing six-month data would permit reasonable assurance of safety and effectiveness.

2c. A subgroup analysis performed on those patients with Class III/IV heart failure showed a more favorable outcome in the secondary endpoints. Please discuss whether the data in the PMA provide reasonable assurance of safety and effectiveness in the subgroup of patients with Class III/IV heart failure.

The panel consensus was that the data did not provide reasonable assurance of safety and effectiveness in this subgroup.

3a. Please comment on the improvement in functional status, quality of life, and six-minute hall walk, and NYHA functional class for the control group as it relates to the improvement in the treatment group and if this relationship changes with the subgroup analysis of patient with advanced heart failure.

The panel was not sure what this improvement in control signified, saying that it might mean the study was underpowered or it might be a result of good medical care, more aggressive treatment, and better medication.

3b. Please comment on the clinical relevance that this finding has on the observed effectiveness of cardiac resynchronization therapy.

The panel thought that the clinical relevance of this finding makes the data more difficult to analyze.

4. Please discuss whether the data in the PMA provide reasonable assurance of effectiveness for this device in the patient population studied.

The panel deferred answering this question.

5a. Is the indications portion of the labeling supported by the data provided? Please comment on whether the indication statement identifies the appropriate patient population for treatment with this device.

The panel found it hard to see the relevance of this question given their efficacy concerns.

5b. Please comment on the operator instructions as to whether they adequately describe how the device should be used to maximize the benefits and minimize adverse events.

The panel had no comments.

5c. Please provide any other recommendations or comments regarding the labeling of this device.

The panel had no comments.

6. Please identify and discuss the items that you believe should be contained in a physician's training program for this device. For example, please comment on whether training should be required for proper placement of the Easy Trak lead system.

The panel had no comments.

7. Do you believe that additional clinical follow-up of postmarket studies are necessary to evaluate the long-term effects of biventricular pacing on heart failure?7a. If so, how you would design such a study, including study design, sample size, patient characteristics, and potential endpoints?

The panel deferred discussion of this question.

Closing Sponsor and FDA Comments

The sponsors and FDA representatives had no additional remarks.

Consumer Representative Robert Dacey noted that the patient information booklet contains overwhelming amounts of information and that patients need one-on-one training with such complicated devices.

Open Public Hearing

There were no requests to address the panel.

Panel Executive Secretary Megan Moynahan read the panel the voting options and instructions.

A motion was made and seconded to recommend the PMA as not approvable. There was discussion about whether it would be better to recommend the PMA as approvable with conditions that further study be performed and the labeling changed. The motion to recommend the PMA as not approvable passed by a vote of six to two, with Drs. Haigney and Aziz voting against the motion. Panel suggestions for putting the PMA into approvable form

were to collect more compelling and comprehensive data, to focus on the highest risk population, to use a composite endpoint, and to build on what has already been done with creative approaches to the data already collected. **Industry Representative Michael C. Morton** recommended holding the company to a standard of six-month follow-up only, with postmarketing data providing further information.

Open Public Hearing

There were no requests to address the panel.

After an adjournment for lunch, **Panel Chair Dr. Swain** reconvened the meeting and read the charge for the afternoon session, which was to consider a PMA for the Medtronic InSync device.

Sponsor Presentation--P010015 Medtronic Corporation's InSync Atrial Synchronous Biventricular Pacing Device and Attain Lead

Marshall Stanton, M.D., medical director of Medtronic, introduced the sponsor representatives and provided introduction and background on CRT via atrial synchronous, biventricular pacing for moderate to severe heart failure patients with ventricular dyssynchrony. He described the device, which consists of the InSync Model 8040, the Attain LV Model 2187, and the Attain CS Model 2188.

William T. Abraham, M.D., explained the design and methodology of the study, which sought to compare the effect of CRT versus no CRT on exercise capacity, quality of life, and functional status in patients with chronic heart failure and ventricular dyssynchrony and to

assess the safety of CRT using the InSync system in patients with chronic heart failure. He described the study population and its drug regimen as well as blinding procedures. Dr. Stanton explained that the control group had atrial tracking but no ventricular pacing unless the patient was in trouble, while the CRT group had atrial tracking and biventricular pacing. He outlined the study phases and patient randomization procedures and listed five primary safety objectives and three secondary safety objectives such as freedom from device-related complications and implant success. Efficacy objectives included change in six-minute hall walk, QOL score, and NYHA class as well as evaluations of metabolic exercise, echocardiographs, QRS duration, and neurohormone evaluation. Patient demographics showed both groups were typical patients of moderate to severe heart failure. Patients were treated with optimal medical treatment at randomization and stability was maintained throughout the study.

Anne B. Curtis, M.D., of the University of Florida, presented the primary safety results. After defining complications and showing a video of the implant procedure, Dr. Curtis presented data to show that the study achieved all primary six-month safety objectives including implant success and freedom from InSync model-related complications, LV lead-related complications, and InSync system-related complications at the six-month point. The Attain model leads achieved performance objectives for the six-month pacing threshold. Dr. Curtis also explained the objectives and methods of the proposed training program.

Dr. Abraham presented efficacy results. On change in distance walked in six minutes, the data showed little placebo effect in the control group and a highly significant improvement in the resynchronization group. On change in quality of life scores, there was a marked placebo effect in the control group, but the CRT group showed a highly significant benefit that exceeded the placebo benefit. Data on change in NYHA functional class at six months showed a highly favorable effect of resynchronization therapy. Thus, each of the primary efficacy objectives was met. Secondary efficacy results showed favorable effects of CRT on change in cardiopulmonary exercise results, change in all measures of echo parameters, change in QRS duration, but no statistically significant difference between control and CRT groups for neurohormones. Dr. Abraham explained the composite response definition and showed that the composite response results highly favors improved outcome for resynchronization therapy.

Secondary safety results showed that patient survival data was much as expected, with no significant differences in causes of death or six month patient survival or complications. Dr. Abraham concluded that CRT is effective in NYHA class II and IV patients because the study used standard heart failure endpoints and demonstrated remarkable consistency across all endpoints, with improvements seen as an adjunct to standard heart failure medications and positive results seen despite the expected placebo effect. He presented data to show that the magnitude of that effect compares well with other proven therapies, such as ACE-I, beta blockers, or digoxin.

FDA Presentation

Mitchell J. Shein introduced the PMA review team and summarized the regulatory history of the device. He listed the InSync components and described preclinical hardware testing and software verification, as well as preclinical testing on the Attain Model 2187-2188 leads, all of which produced satisfactory results.

Helen S. Barold, M.D., gave the clinical summary. She read the proposed indications for use, reviewed the study methodology, and listed the primary and secondary effectiveness endpoints and primary and secondary safety objectives. After explaining inclusion and exclusion criteria and patient baseline characteristics, Dr. Barold discussed patient randomization that resulted in six-month paired data on 170 control and 174 CR patients.

Dr. Barold presented data showing change in NYHA classification from baseline to six months for both control and treatment group, with improvement significantly favoring the treatment group. Quality of life results were also highly significant for the treatment over control group, with a nine-unit difference in improvement. The six-minute hall walk results also significantly favored the treatment group, with a 30- meter difference in improvement.

Functional effectiveness endpoints showed improvements in the treatment group for QRS duration, peak VO₂, and exercise time. Echo parameters were variable but did improve in the treatment group. There was no difference in healthcare utilization and change in only one neurohormone level. Safety data showed no difference in mortality or patient survival to six months. The implant had a 92% implant success rate and two complications involving the

generator only of the InSync model. Coronary sinus trauma data showed a 6% rate. Freedom from complications for the system and the lead were above 90% for all complications. Lead results met safety and n lead performance endpoints, as well as showing adequate electrical performance. Dr. Barold concluded that the device met safety, lead performance endpoints, and primary effectiveness endpoints. Mitchell Shein read the FDA questions for panel discussion.

Open Committee Discussion

Dr. Swain thanked the sponsors and FDA presenters. **Dr. Ileana Pina** began the panel discussion by asking a number of questions about blinding procedures and about the use of beta blockers or defibrillators with the patient population. She urged sponsors to continue to look for echo data in both groups and to monitor mortality in the long-term follow-up. In general, the panel complimented the sponsors on a well-performed study that showed a substantial effect for the device over control. **Consumer Representative Robert Dacey** stated that he was impressed with the patient education materials. Other panel members urged that the sponsors not provide the leads to individuals or sponsors who had not taken the sponsor-provided training and that sponsors continue to complete the data sets. The sponsor agreed that leads would not be provided to individuals not completing the training.

FDA Questions

1a. Please discuss potential safety issues associated with implantation a lead in the coronary venous system and comment on whether the data in the PMA support the safety of the lead system for the proposed indication.

The panel saw no worrisome issues concerning lead safety or the data provided to support such safety.

1b. Please discuss the clinical importance of the overall adverse events, complications, and observations, and comment on whether the data in the PMA provide reasonable assurance of the safety of this device system.

The panel agreed that the data in the PMA provide reasonable assurance of the safety of this device system.

2a. Please discuss the clinical relevance of the effectiveness endpoints for this patient population.

The panel agreed that while the effectiveness endpoints were “soft,” they were relevant to the clinical enterprise of the study.

2b. Please comment on whether six-month follow-up is adequate to assess safety and effectiveness in this patient population.

The panel thought that six-month followup is adequate, although a more sustained follow-up on mortality is very important in general in all trials. They would also like to see data on those who deteriorate or do not benefit from the device.

3a. The control group saw an improvement in their NYHA class, QOL score, and six-minute hall walk. Please comment on this improvement in the control group.

The panel had no additional comments on this issue.

3b. Please discuss whether the magnitude of the difference between the control and treatment groups is clinically meaningful.

The panel agreed that the magnitude of the difference between control and device group is meaningful, although it is a challenge to quantify that benefit in the labeling and to convey the need for careful patient enrollment to the broader universe.

4. Please discuss whether the data in the PMA provide reasonable assurance of effectiveness for this device in the patient population studied.

The panel agreed that the data do provide reasonable assurance of device effectiveness for this population.

5a. Please comment on the operator instructions as to whether they adequately describe how the device should be used to maximize the benefits and minimize adverse events.

The panel recommended more explanation for the technique of implanting the coronary sinus lead in the patient manual, more clarification on the electro-cautery section, and more information in the patient manual about the need for close monitoring for the first few months.

5b. Please provide any other recommendations or comments regarding the labeling of this device.

The labeling must clearly indicate that the indication is for patients who are refractory to stable medical treatment and that it is for symptomatic relief associated with congestive heart failure, not for prolongation of life or cure of heart failure. Primary care physicians should be educated about the need to refer such patients to heart failure specialists, who can determine that the patient has not achieved the stable medical treatment described.

6. Please identify and discuss the items that you believe should be contained in a physician's training program for this device. For example, please comment on whether training should be required for proper placement of the Attain 2187/2188 lead system.

Electrophysiologists should be educated about ensuring the patients are well medicated for this procedure. Physician training should be mandatory for all those wishing to purchase the device. The sponsors were also complimented on not using animal models for training.

7a. Do you believe that additional clinical follow-up of postmarket studies are necessary to evaluate the long-term effects of biventricular pacing on heart failure? If so, please discuss how you would design such a study, including a study design, sample size, patient characteristics, and potential endpoints.

The panel thought ongoing surveillance of this cohort is important, although there was disagreement about the need for a formal study. One member suggested a study focused on mortality and of the qualitative functional endpoints at one to three years. Looking at 12-month survival and echo data was also recommended. It was noted that long-term follow-up on the leads is important.

7b. In support of Medtronic's proposed indications for use, multiple subgroup analyses have been performed. Please comment on the clinical relevance of these analyses and whether this information is appropriate for inclusion in the label or should be the basis for postapproval studies or both.

The panel did not further address this issue.

Recommendations and Voting

Panel Executive Secretary Megan Moynahan read the voting instructions and options.

A motion was made and seconded to recommend the motion as approvable with conditions.

The conditions were as follows:

1) The remaining six-month data on the 37 and 41 patients in each group should be acquired.

This condition passed unanimously.

2) Six-month echo data should be completed for the database. This condition passed unanimously.

3) A mortality assessment should be done on an intent-to-treat analysis, and an ongoing follow-up of the existing IDE cohort should be performed. This motion passed by a vote of five to two.

4) The modifications to labeling and to the physician patient instruction booklets should be made as discussed by the panel. This motion passed unanimously.

The vote to recommend the PMA as approvable subject to conditions passed unanimously.

Open Public Hearing

There were no requests to address the panel.

Dr. Swain adjourned the Open Session at 5:00 p.m.

I certify that I attended the Open Session of the Circulatory Systems Devices Panel Meeting on July 9-10, 2001, and that this summary accurately reflects what transpired.

Megan Moynahan.
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

Cynthia M. Tracy, M.D.
Chairperson (July 9, 2001 only)

Julie Swain, M.D.
Acting Chairperson (July 10, 2001 only)

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